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Date September 18, 2000

To Examiner James Ketter  
Art Unit 1636  
U.S. Patent and Trademark Office

Facsimile number 07236-01300004 / 703-305-7939

From Janis K. Fraser, Ph.D., J.D.

Re U.S. Patent Application No. 09/225,718  
Applicant: Douglas A. Treco et al.  
Filing Date: January 6, 1999  
Attorney/Docket No.: 07236-013004

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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Douglas A. Treco et al.  
Serial No. : 09/225,718  
Filed : January 6, 1999  
Title : TRANSKARYOTIC PRODUCTION AND DELIVERY OF DNASE

Art Unit : 1636  
Examiner : J. Ketter

Commissioner for Patents  
Washington, D.C. 20231

THIRD PRELIMINARY AMENDMENT

Prior to examination, please amend the application as follows:

In the Claims:

Cancel claims 58-65 without prejudice. Add the following new claims.

66. A method of providing a therapeutic product to a mammal, comprising introducing into the mammal a vertebrate cell which produces the therapeutic product, the cell being generated by an *in vitro* process comprising:

(a) providing a vertebrate cell the genomic DNA of which comprises an endogenous gene;

(b) providing a DNA construct comprising:

(1) a targeting sequence homologous to a target site within or upstream of the endogenous gene,

(2) an exogenous regulatory sequence,

(3) an exon, and

(4) an unpaired splice-donor site at the 3' end of the exon; and

(c) transfecting the vertebrate cell with the construct, thereby generating a homologously recombinant cell in which the exogenous regulatory sequence controls expression of a transcript comprising sequence corresponding to the construct-derived exon, the construct-derived splice-donor site, and all endogenous exons of the endogenous gene to produce an RNA transcript that encodes the therapeutic product.

67. The method of claim 66, wherein the vertebrate cell is a primary or secondary cell.

68. The method of claim 67, wherein the primary or secondary cell is a mammalian cell.

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